Effect of cardiac resynchronization therapy on the incidence of ventricular arrhythmias in patients with an implantable cardioverter-defibrillator

Arash Arya, MD, Majid Haghjoo, MD, Mohammad Reza Dehghani, MD, Mohammad Alasti, MD, Hormoz Alizadeh, MD, Babak Kazemi, MD, Mohammad Ali Sadr-Ameli, MD

From the Department of Pacemaker and Electrophysiology, Rajaie Cardiovascular Medical and Research Center, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.

BACKGROUND Cardiac resynchronization therapy (CRT) reduces mortality in selected patients with heart failure. However, this result may not be entirely related to the beneficial hemodynamic effects of CRT.

OBJECTIVES The purpose of this study was to assess retrospectively the effect of CRT on the incidence of appropriate therapy in patients with an implantable cardioverter-defibrillator (ICD).

METHODS Sixty-five patients (48 men and 17 women; mean age 58 ± 13 years) with an ICD (31 biventricular, 34 dual-chamber) were included in the study. Clinical, ECG, and ICD stored data and electrograms were collected.

RESULTS Biventricular and dual-chamber ICDs were implanted in 31 and 34 patients, respectively, who had either ischemic (n = 36) or dilated cardiomyopathy (n = 29). Thirty-two (49%) patients received ≥1 appropriate ICD therapy during follow-up of 11 ± 8 months. Thirty-five percent and 62% of patients with biventricular (n = 11) and dual-chamber ICDs (n = 21), respectively, received appropriate ICD therapy during the follow-up period (odds ratio = 0.340, $P = .048$). Stratifying the patients according to underlying heart disease and ejection fraction resulted in an adjusted odds ratio = 0.239 ($P = .029$). Comparing the rate of ≥1 appropriate ICD therapy between the two groups by Kaplan-Meier analysis and the log rank test resulted in $P = .027$.

CONCLUSION In this retrospective analysis, biventricular pacing was associated with a decreased incidence of sustained ventricular arrhythmias requiring ICD therapy. The antiarrhythmic effect of biventricular pacing could contribute to the reduction in mortality reported in recent large-scale clinical trials on CRT. However, further prospective studies are warranted to clarify this issue.

KEYWORDS Cardiac resynchronization therapy; Implantable cardioverter-defibrillator; Ventricular arrhythmia; Heart failure

(Heart Rhythm 2005;2:1094–1098)

Introduction

Cardiac resynchronization therapy (CRT) is an established mode of therapy in selected symptomatic patients with heart failure due to systolic dysfunction.[1] Recent large-scale clinical trials of CRT have confirmed the favorable effects of CRT on symptoms, quality of life, ventricular function, and blood pressure and showed that CRT significantly reduces mortality risk.[2,3] Calculations based on data from the Cardiac Resynchronization–Heart Failure trial showed that for every nine biventricular pacemaker implanted, one death and three hospitalizations for major cardiovascular events were prevented.[2] The reduction in mortality by CRT is at least partly related to hemodynamic improvement.[1]

Some experimental studies have suggested that epicardial pacing of the left ventricle in CRT prolongs the QT interval and increases the transmural dispersion of refractoriness.[4] In addition, some cases of increased ventricular arrhythmias following CRT have been reported.[5,6] How-

Address reprint requests and correspondence: Dr. Arash Arya, Department of Pacemaker and Electrophysiology, Rajaie Cardiovascular Medical and Research Center, School of Medicine, Iran University of Medical Sciences, Mellat Park, Vali-Asr Avenue, Tehran, 1996911151, Iran.

E-mail address: dr.arasharya@gmail.com.

(Received May 9, 2005; accepted July 10, 2005.)

  doi:10.1016/j.hrthm.2005.07.007

Table 1 Baseline characteristics of patients

Variables	ICD-DR†	CRT-D¶	P-Value
Number	34	31	—
Follow-up period	11 ± 8	10.3 ± 6	0.455
Age (year)	57 ± 13	58 ± 12	0.849
Sex:			
Male	26 (76%)	22 (71%)	0.614
Female	8 (34%)	9 (29%)	
Underlying heart disease:			
Coronary artery disease	24 (70%)	12 (39%)	0.013
Dilated cardiomyopathy	10 (30%)	19 (61%)	
LVEF* (%)	26 ± 8	22 ± 6	0.013
QRS duration (ms)	146 ± 30	149 ± 25	0.711
Corrected QT interval (ms)	480 ± 58	473 ± 68	0.631
Indication of ICD implantation (n):			
Primary prevention	11	10	0.484
Secondary prevention	23	21	
Beta-blocker therapy (%)	53%	40%	0.250
ACE‡ Inhibitors	88%	83%	0.371
Amiodarone	62%	53%	0.409

*Left ventricular ejection fraction.
†Dual chamber implantable cardioverter-defibrillator.
‡Angiotensin converting enzyme.
¶Implantable cardioverter-defibrillator with biventricular pacing option.

ever, several clinical studies have suggested the opposite, showing that CRT reduced mortality by decreasing the incidence of lethal ventricular arrhythmias.[7–14]

We conducted a retrospective case-control study to assess the effect of CRT on the incidence of appropriate therapy as a surrogate for sustained ventricular arrhythmias (see Definitions) in patients with an implantable cardioverter-defibrillator (ICD).

Methods

Patient population

Between December 2002 and February 2005, 31 patients underwent transvenous biventricular ICD placement at our center. The left ventricular lead was implanted via thoracotomy in two patients. All patients had QRS width ≥120 ms and standard indication for CRT[1] and ICD placement (see Definitions). During the same period, 68 patients with coronary artery disease or dilated cardiomyopathy received a dual-chamber ICD at our center. From among these 68 patients, all individuals with QRS duration ≥120 ms (n = 34) were selected as the control group. Bradycardia pacing of dual-chamber ICDs was programmed to VVI with a rate of 40 bpm to prevent unnecessary ventricular pacing, except in patients with established indications for cardiac pacing (n = 5).[15] All patients gave written informed consent for ICD placement. Mean patient age was 58 ± 13 years. Basic characteristics of the patients are given in Table 1.

ICD data storage and retrieval

After ICD placement, patients were followed on a regular basis (3 months) and upon receiving high-voltage therapy in our outpatient ICD clinic. The devices were interrogated at each session, and the complete set of data (including intracardiac electrograms) was recorded on floppy diskettes. The summary of the episodes also was recorded in the patient's file. The floppy diskettes were used in this study to retrieve all sustained arrhythmia episodes. Each episode was studied by two independent electrophysiologists (AA and MRD) to define the diagnosis. In case of a discrepancy in diagnosis, the final analysis of the arrhythmia episode was made by a consensus of three electrophysiologists (AA, MRD, and MH). In addition to the diagnosis, the time of arrhythmia after implantation and the mode of therapy were recorded.

Definitions

Appropriate ICD therapy was defined as antitachycardia pacing or shock therapy for ventricular tachycardia (VT) or ventricular fibrillation (VF). All patients who received biventricular ICDs had standard indications for ICD placement.[16] *Indication for ICD placement* was defined as *secondary prevention* (n = 44) in patients who had experienced aborted sudden cardiac death, sustained ventricular arrhythmia, or syncope (n = 9 with structural heart disease whose electrophysiologic study showed inducible, sustained, hemodynamically unstable ventricular arrhythmias). The indication for ICD placement was categorized as *primary prevention* in all other patients (n = 21 with Multicenter Automatic Defibrillator Implantation Trial [MADIT], Multicenter Unsustained Tachycardia Trial [MUSTT]-like indications, i.e., patients with coronary artery disease [n = 10] and asymptomatic patients with dilated cardiomyopathy [n = 11] with nonsustained VT during Holter monitoring who had inducible, sustained, hemodynamically unstable ventricular arrhythmia during electrophysiologic study).[16]

Statistical analysis

Variables are expressed as mean ± SD and percentage. Differences in the frequency of characteristics were assessed by independent sample Student's t-test for continuous variables. Chi-square test (or Fisher exact test if applicable) was used for discrete variables. Probability of ≥1 appropriate ICD therapy based on the time to first appropriate ICD therapy between the two groups was determined by Kaplan-Meier analysis with Mantel-Cox (log rank) test. The time to first appropriate ICD therapy was plotted according to the Kaplan-Meier method. The Mantel-Haenszel test was used to generate the P value for reported odds ratios. Two-tailed $P < .05$ was considered significant. SPSS 13.0 software (SPSS Inc., Chicago, IL, USA) was used for data storage and analysis.

Results

Baseline characteristics

Sixty-five patients with biventricular and dual-chamber ICDs were followed for a mean 11 ± 8 months. Biventricular and dual-chamber ICDs were placed in 31 and 34 patients, respectively. Characteristics of the patients with the two types of ICDs were compared (Table 1). Patients with biventricular ICDs had lower left ventricular ejection fraction (22 ± 6 vs 26 ± 8, $P = .013$) and higher prevalence of dilated cardiomyopathy as the underlying heart disease (61% vs 30%, $P = .013$). Other variables between the two groups were comparable.

Appropriate ICD therapy

Thirty-two patients (49%) received ≥1 appropriate ICD therapy during the follow-up period. VT and VF (based on detection zones) were responsible for the first appropriate ICD therapy in 20 (62.5%) and 12 (27.5%) patients, respectively. The proportion and cycle length of these ventricular arrhythmias were comparable between the two groups (all P = NS).

Thirty-five percent and 62% of patients with biventricular (n = 11) and dual-chamber ICDs (n = 21), respectively, received appropriate ICD therapy during the follow-up period (odds ratio = 0.340, 95% confidence interval = 0.125–0.935, $P = .048$). The mean number of appropriate ICD therapies in patients with dual-chamber and biventricular ICDs was 13 ± 32 (range 0–132) and 1.3 ± 2.5 (range 0–9), respectively ($P = .047$).

Interaction between ICD type and probability of ≥1 appropriate ICD therapy

Figure 1 shows the comparison of differences in ≥1 appropriate ICD therapy using Kaplan-Meier survival curves for the two device groups, with application of Mantel-Cox (log rank) test ($P = .027$). Among 34 patients with dual-chamber ICDs and 31 patients with biventricular ICDs, 62% and 35% received appropriate ICD therapy, respectively (odds ratio = 0.340, 95% confidence interval = 0.125–0.935, $P = .048$). Analysis was repeated by stratifying patients according to underlying heart disease and left ventricular ejection fraction. The subgroups of left ventricular ejection fraction were divided based on the median value (25%) in the study population. The adjusted odds ratio was 0.239 (95% confidence interval = 0.1–0.84, $P = .029$).

Prevalence and number of nonsustained VTs

Forty-eight patients (74%) had nonsustained VT during the follow-up period. A trend toward higher prevalence of nonsustained VT in patients with dual-chamber ICDs vs those with biventricular ICDs (80% vs 68%) failed to reach statistical significance ($P = .258$). A trend toward a higher mean number of nonsustained VTs in patients with dual-chamber ICDs (155 ± 394 [range 1–1,642] vs 33 ± 95 [range 1–436]) also failed to reach statistical significance ($P = .113$).

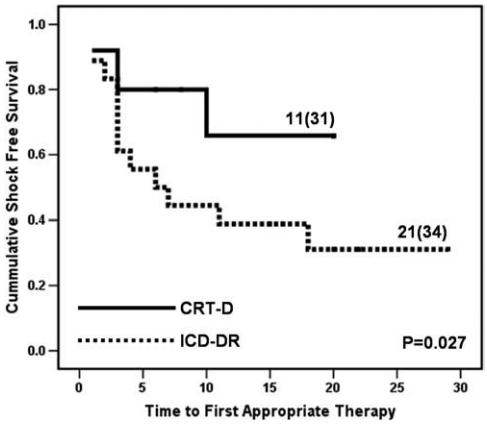

Figure 1 Kaplan-Meier plot of the time to the first inappropriate therapy according to ICD type. Log rank (Mantel-Cox) test was used to generate the P value. CRT-D = biventricular implantable cardioverter-defibrillator; ICD-DR = dual-chamber implantable cardioverter-defibrillator.

We assumed that the differences in baseline characteristics may have biased these findings (Table 1). To adjust for differences in baseline characteristics, we divided the patients into two groups based on the median number of nonsustained VTs in the cohort (median = 3) and repeated the analysis by stratifying for ejection fraction and underlying heart disease. This analysis yielded an adjusted Mantel-Haenszel $P = .059$ ($\chi^2 = 3.561$). A correlation was found between total number of nonsustained VTs and total number of appropriate ICD therapies (Pearson r = 0.964, $P < .01$).

Discussion

Main findings

Biventricular pacing decreased the rate of appropriate ICD therapy (including both antitachycardia pacing and shock) by suppressing the occurrence of sustained ventricular arrhythmias requiring ICD therapy. During the follow-up period, patients with biventricular ICDs received 66% fewer appropriate ICD therapies compared to patients with dual-chamber ICDs (Figures 1 and 2).

The recent clinical trials on CRT confirmed that CRT significantly reduces the risk of death.[2,3] However, the reduction in mortality may not be related entirely to the favorable hemodynamic effects of CRT. Several potential mechanisms may explain the observed antiarrhythmic effect of CRT.

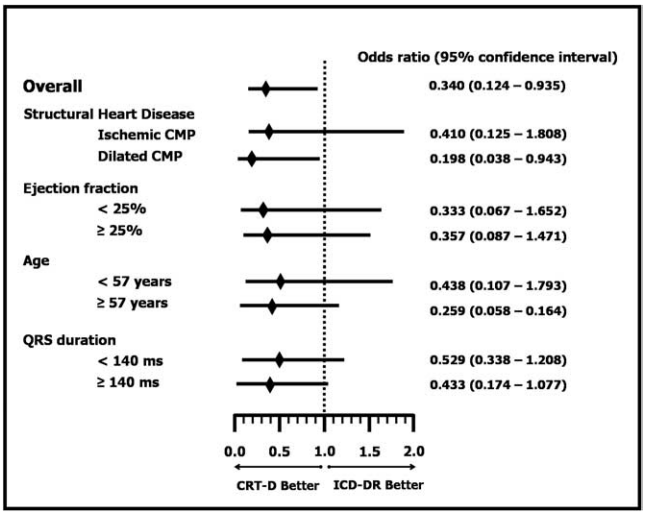

Figure 2 Effect of biventricular pacing on the incidence of appropriate implantable cardioverter-defibrillator (ICD) therapy. Unadjusted odds ratios and 95% confidence intervals are shown. The subgroups of age, ejection fraction, and QRS width are divided based on the median values of the study population. CRT-D = biventricular implantable cardioverter-defibrillator; ICD-DR = dual-chamber implantable cardioverter-defibrillator.

Although we did not assess the hemodynamic response to CRT in our study, improvement in left ventricular performance could partly explain the decreased incidence of appropriate ICD therapy in patients with biventricular ICDs.[14,17,18] Hemodynamic improvement following CRT could decrease the stretch on myocardium and modulate autonomic nervous system activity, which in turn would reduce the incidence of lethal ventricular arrhythmias.[14,18] Several studies have shown that biventricular pacing decreases the frequency of ventricular ectopy.[7,10] Reducing ventricular ectopy that can trigger sustained ventricular arrhythmias could decrease the incidence of sustained ventricular arrhythmias and appropriate ICD therapy.

Several studies have shown that biventricular pacing reduces the inducibility of VT.[9–11] Kowal et al[9] evaluated the acute electrophysiologic effects of biventricular pacing in a prospective randomized study. They showed that biventricular compared with right ventricular programmed electrical stimulation significantly reduced induction of VT (but not VF). They hypothesized that the mechanism of arrhythmia suppression by biventricular pacing was preexcitation of the area of slow conduction responsible for reentrant arrhythmias and significant increase in the local left ventricular coupling interval.[9]

Experimental studies have suggested that epicardial left ventricular pacing increases the transmural dispersion of refractoriness, hence biventricular pacing may cause proarrhythmia in selected patients with CRT.[4,14] Berger et al[13] assessed the effect of biventricular pacing on ECG markers of ventricular repolarization in patients with congestive heart failure. Using high-resolution surface ECG, they showed that biventricular pacing significantly reduced ECG markers of ventricular dispersion of repolarization, which could contribute further to the antiarrhythmic effects of CRT.

In a similar study to ours, Higgins et al[7] showed that appropriate ICD therapy was less common with biventricular ICDs in patients with standard indications for ICDs. However, several points merit consideration. All left ventricular leads were placed via thoracotomy in the study by Higgins et al, whereas left ventricular leads were positioned via the coronary sinus in all but two of our patients. In the study by Higgins et al, only 32 of 54 patients (59%) were suitable for the final paired analysis, and the period of observation in each mode of pacing was only 3 months.[17] Our study with a larger patient population confirmed the beneficial effect of biventricular pacing in reducing appropriate ICD therapy during a longer follow-up period. However, ICD therapy should not be equated with a reduction in sudden cardiac death. Therefore, larger prospective studies with cardiac and all-cause mortality as the endpoints are warranted to clarify this issue.

Although the bulk of evidence favors antiarrhythmic effects of CRT,[7–14] several case reports have shown an increased incidence of ventricular arrhythmia following biventricular pacing or ICD placement.[5,6] In addition, despite a statistically significant lower absolute number of deaths classified as sudden in the CRT group compared with the control group in the Cardiac Resynchronization–Heart Failure study, the proportion of deaths that were classified as sudden cardiac death was comparable between the two groups. The mode of death was classified as sudden in 38 of the 120 patients (32%) who died in the medical therapy group and in 29 of the 82 patients (35%) who died in the CRT group.[2]

Although the underlying mechanism(s) in the case reports mentioned are not clear, physicians should be aware of occasional proarrhythmic effects of CRT. Biventricular pacing-induced VT is one of the study endpoints of PACMAN (Pacing for Cardiomyopathies, a European study), a prospective single-blind study ongoing in Europe. This study will help determine the incidence of biventricular pacing-induced VT.[6]

Clinical implication

The antiarrhythmic effect of biventricular pacing could contribute to the reduction in mortality observed in CRT patients.

Study limitation

We did not record and assess the effect of New York Heart Association (NYHA) functional class on the rate of appropriate ICD therapy. Patients are more likely to receive appropriate ICD therapy if they have lower left ventricular ejection fraction and higher NYHA functional class.[7] Although we adjusted our analyses for ejection fraction, we did not record the NYHA functional class of the patients.

This could have resulted in underestimation of the beneficial effect of CRT on the incidence of ventricular arrhythmias during follow-up, as we would expect a higher NYHA functional class in the biventricular ICD group. Finally, it is possible that after VT detection and appropriate ICD discharge, electrical and/or medical treatment was adjusted or optimized to prevent new VT recurrences. However, to minimize this effect, we only compared the occurrence of $\geq$1 appropriate ICD therapy between the two groups rather than the total number of appropriate ICD therapies.

Conclusion

In selected patients with heart failure with standard indications for ICD placement, biventricular pacing reduced the incidence of appropriate ICD therapy as a surrogate for sustained ventricular arrhythmias. Further large-scale prospective studies assessing the potential antiarrhythmic effects of CRT are warranted.

Acknowledgments

We thank Mohammad-Hossein Nikoo, MD, without whose dedicated help in our outpatient ICD clinic this study as presented would have not been possible. We also thank Elham Hasheminejad, MD, for assistance with editing the manuscript.

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